Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki disease

RAISE Study

Study Protocol for the RAISE Study

- Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki disease -

This study is supported by the Ministry of Health, Labour and Welfare (MHLW), Health and Labour Sciences Research Grants for the Comprehensive Research on Practical Application of Medical Technology:

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1. RESEARCH GOALS

This study will investigate whether initial treatment with high-dose intravenous immunoglobulin plus prednisolone (PSL) yields better results than standard treatment (high-dose intravenous immunoglobulin) in patients with Kawasaki disease (KD). The primary endpoint of this study is incidence of coronary artery abnormalities (CAA) during the study period. The secondary endpoints include incidence of CAA at 4 weeks after enrollment, Z scores for the right coronary artery and left main coronary trunk and anterior descending artery, days of fever after enrollment, incidence of need for additional rescue therapy, serum levels of C-reactive protein (CRP) at Weeks 1 and 2 after enrollment, and incidence of severe adverse events.

2. BACKGROUND AND RATIONALE FOR THE STUDY

2.1. Subjects

2.1.1. Disease studied and current standard treatment

KD is a vasculitis syndrome of unknown cause, first reported by Tomisaku Kawasaki in 1967.[1] It is the leading cause of acquired heart disease in developed countries.[2] Because the causes of KD have not been identified, there are no specific therapies for KD patients. Furusho et al[3] in 1984 and Newburger et al[4] in 1986 reported that treatment with intravenous immunoglobulin (400 mg/kg×4 or 5 days) plus aspirin reduced the incidence of CAA as compared with aspirin alone (Furusho: 19/45 [42%] vs. 6/40 [15%]; Newburger: 14/79 [18%] vs. 3/79 [4%]).

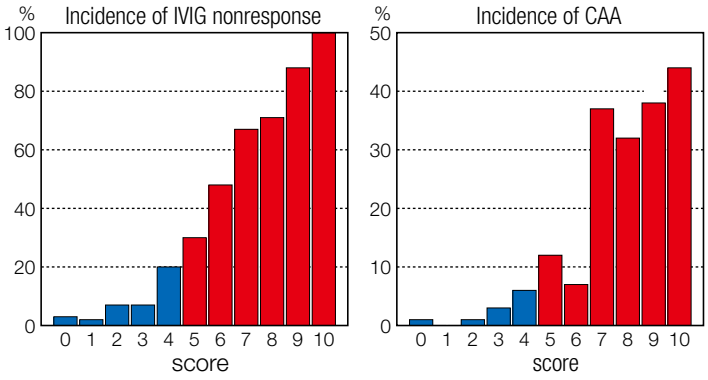
In 1991, Newburger et al[5] reported the efficacy of high-dose intravenous immunoglobulin (2 g/kg×single day) plus aspirin therapy: the relative risk of CAA formation was 1.94 (95%CI 1.01-3.71) at Week 2 and 1.84 (95%CI 0.89-3.82) at Week 7. Since then, high-dose intravenous immunoglobulin plus aspirin therapy (IVIG) has become the standard therapy for acute KD.[6] IVIG is clearly effective and has adequate safety. However, approximately 20% of KD patients did not become afebrile despite IVIG administration[7)-9)]; those IVIG nonresponders are considered to be at high risk for CAA. These facts suggest the importance of establishing a new therapeutic strategy for severe KD patients, particularly IVIG nonresponders.

2.1.2. Reasons for selection of subject groups

IVIG is an excellent therapy in resolving inflammation from KD and reducing the occurrence of CAA. However, approximately 20% of KD patients have persistent or recurrent fever after IVIG; further, many studies have shown that these patients are at increased risk of developing CAA. Early identification of likely IVIG nonresponders who will require additional therapy

might reduce the risk of coronary artery injury. For this purpose, Kobayashi et al[10] developed a risk score to predict IVIG nonresponse among KD patients before the initiation of IVIG.

Characteristic	Threshold value	Points
Sodium	≤133 mmol/L	2
AST	≥100 IU/L	2
Days of illness at diagnosis	4 illness days	2
% neutrophils	≥80%	2
CRP	≥10 mg/dL	1
Age in months	≤12 months	1
Platelet count	≤300,000/mm^3	1



Using this risk score, KD patients can be stratified as being at high (5 points or more) or low risk (4 points or less) for IVIG nonresponse; IVIG nonresponders were identified with a sensitivity of 74% and a specificity of 80%, and CAA was identified with a sensitivity of 77% and a specificity of 71%. The risk score thus might enable us to identify KD patients who require more intensive initial therapy. High-risk patients can then be started on more intensive initial treatments. Moreover, identification of patients for whom standard IVIG will likely suffice allows such patients to be spared unnecessary treatment.

2.2. Rationale for establishing treatment regimen

Corticosteroids are administrated for various forms of vasculitis because of their strong anti-inflammatory effects. However, many physicians have hesitated to use corticosteroids in KD because an early report[11] showed a high incidence of CAA in a group that received a prolonged course of oral PSL alone. However, subsequent retrospective studies[12)-16)] of the effects of corticosteroids in KD have shown either no adverse effects or possible benefits. Wooditch and Aronoff[17] concluded in a meta-analysis that inclusion of corticosteroids in aspirin-containing regimens for initial therapy of KD reduced the incidence of CAA.

In 2006, Inoue et al[18] reported in a randomized, open-label, unblinded trial that IVIG plus PSL therapy decreased the incidence of CAA and treatment nonresponse, although potential methodological flaws were noted in the study.[19] In 2007, Newburger et al[20] conducted a randomized, double-blinded, placebo-controlled trial of the efficacy of adding a single dose of pulsed intravenous methylprednisolone to conventional IVIG therapy. Although pulsed corticosteroid therapy with IVIG did not improve coronary artery outcomes, post-hoc subgroup analysis suggested that initial therapy with intravenous methylprednisolone plus IVIG might provide a benefit for children at highest risk for resistance to initial IVIG.

The principal difference between the 2 studies was the duration of corticosteroid administration.

Although the total dose of corticosteroids was similar, the median duration of PSL administration was 21 days in the earlier study, as compared with 1 course of 30 mg/kg methylprednisolone in the US study. The serum half-life of a pulsed dose of methylprednisolone is approximately 3 hours[21], and PSL was administered for 3 weeks in the Japanese study. Although KD is self-limiting, fever persists approximately 2-3 weeks if untreated.[1] Duration of corticosteroid administration might be more important than maximum concentration of corticosteroid in suppressing inflammation and vasculitis in KD. Thus, the RAISE Study group selected conventional PSL therapy combined with IVIG plus aspirin, as reported by Inoue et al.

2.3. Study Design

2.3.1. Planned Phase III study design

Interventional, Prospective, Randomized, Open-label, Blinded-Endpoint (PROBE) study

2.3.2. Endpoints

Primary

- Incidence of CAA during the study period

Secondary

- Incidence of CAA at Week 4 after enrollment
- Z scores[22] for right coronary artery and left main coronary trunk and anterior descending artery
- Incidence of need for additional rescue therapy
- Days of fever after enrollment
- Serum levels of CRP at Weeks 1 and 2 after enrollment
- Incidence of severe adverse events

2.3.3. Clinical hypotheses and reason for number of registrants

The principal hypothesis of the present study is that patients with severe KD who receive the study treatment (IVIG with PSL) will have a significantly lower incidence of CAA during the study period as compared with the group receiving standard treatment (IVIG). If this does indeed prove to be true, then initial treatment with IVIG plus PSL will be judged to be more effective.

The target enrollment was set using data obtained from 1123 consecutive KD patients from August 2000 to August 2007 at 13 hospitals in Gunma and Saitama prefectures, Japan.[23] Eight KD patients who presented with CAA at admission and 109 KD patients with missing values were excluded from this study. Thus, data from 1006 KD patients (IVIG group n=896, IVIG+PSL group n=110) were analyzed. Of the 110 patients in the IVIG+PSL group, 90 were participants of a previously reported randomized trial.[18] The other 20 patients were given IVIG+PSL according to the attending doctor's recommendations, except for 1 patient

whose parents desired treatment with IVIG+PSL. The table below shows clinical and coronary outcomes in the high-risk group.

	IVIG (n=298)	IVIG+PSL (n=48)
Nonresponse to treatment	51.7	20.8
Incidence of coronary artery abnormality during 1 month	18.1	6.3
Incidence of coronary artery abnormality at 1 month	8.4	4.2

The primary endpoint of the RAISE Study is to assess whether the incidence of CAA in the study treatment is significantly lower than that of the standard treatment during the study period. Based on the above data, the required sample size was calculated with the assumption that IVIG plus PSL would reduce the fraction of patients with CAA during the study period from 18% to 8%. With a 2-sided test, an α level of 0.05, and a power of 80% and assuming that 10% of the patients would not complete the study, a total sample of 392 patients would be required. Analyses were intent-to-treat. Fisher' s exact test was used to test the null hypothesis, i.e. that the incidence of CAA would be equal between the 2 treatment groups during the study period.

3. DEFINITIONS USED IN THE STUDY

3.1. Diagnosis of KD

A diagnosis of KD is based on the presence of fever accompanied by at least 4 of the following symptoms: bilateral conjunctival injection, changes in the lips and oral cavity, nonpurulent cervical lymphadenopathy, polymorphous exanthema, and changes in the extremities. Patients with incomplete KD (fever with 3 or fewer of the above symptoms) at diagnosis will be enrolled if they receive a diagnosis of KD from the attending physician. These diagnostic criteria comply with the Diagnostic Guidelines for Kawasaki Disease (Fifth Revised Edition).[24)]

3.2. Using risk score to identify severe KD patients

Disease severity will be assessed using the risk score developed by Kobayashi et al.[10)] This risk scoring system was based on a multiple logistic regression analysis of 750 consecutive KD patients given IVIG. Seven variables were included in the risk score. Points are assigned using the threshold values shown below (higher scores indicate greater disease severity).

Variable	Threshold value	Points
Sodium	≤133 mmol/L	2
AST	≥100 IU/L	2
Illness days at diagnosis	≤ 4 illness days	2
%neutrophils	≥80%	2
CRP	≥10 mg/dL	1
Age in months	≤12 months	1
Platelet count	≤300,000/mm^3	1

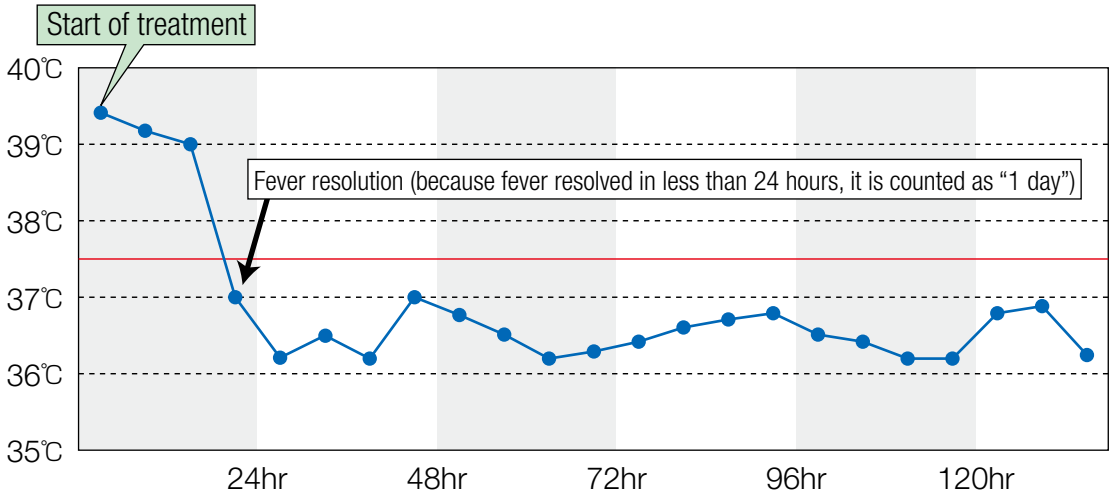
The total number of points assigned to a patient is that patient's risk score. If a laboratory test was performed twice or more before initial therapy, the highest value was chosen for AST, % neutrophils, and CRP, while the lowest value was chosen for sodium and platelet count. In the present study, patients will be defined as high risk if they have a total score of 5 points or higher, and only these high-risk patients will be randomly assigned to the 2 treatment groups.

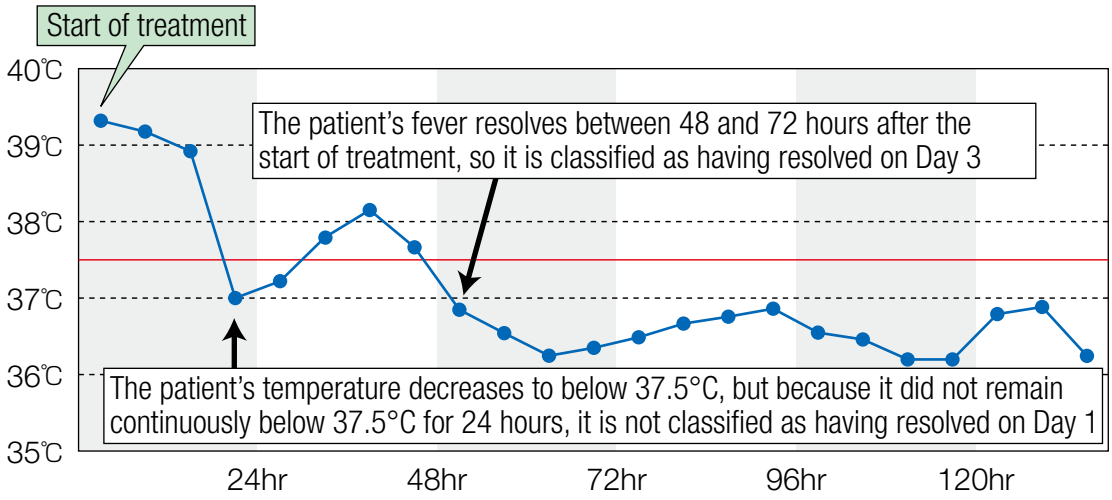
3.3. Definition of fever

Febrile: ≥37.5˚C

Afebrile: ‹37.5˚C for ≥24 hours.

Absence of fever is defined as a body temperature lower than 37.5˚C for at least 24 hours, using an electronic thermometer in the axilla. In calculating time to resolution of fever, start of treatment is defined as Hour 0. Fever resolution within 24 hours is defined as "on the first day," within 48 hours as "on the second day," etc., with subsequent 24-hour periods each counted as a "day."

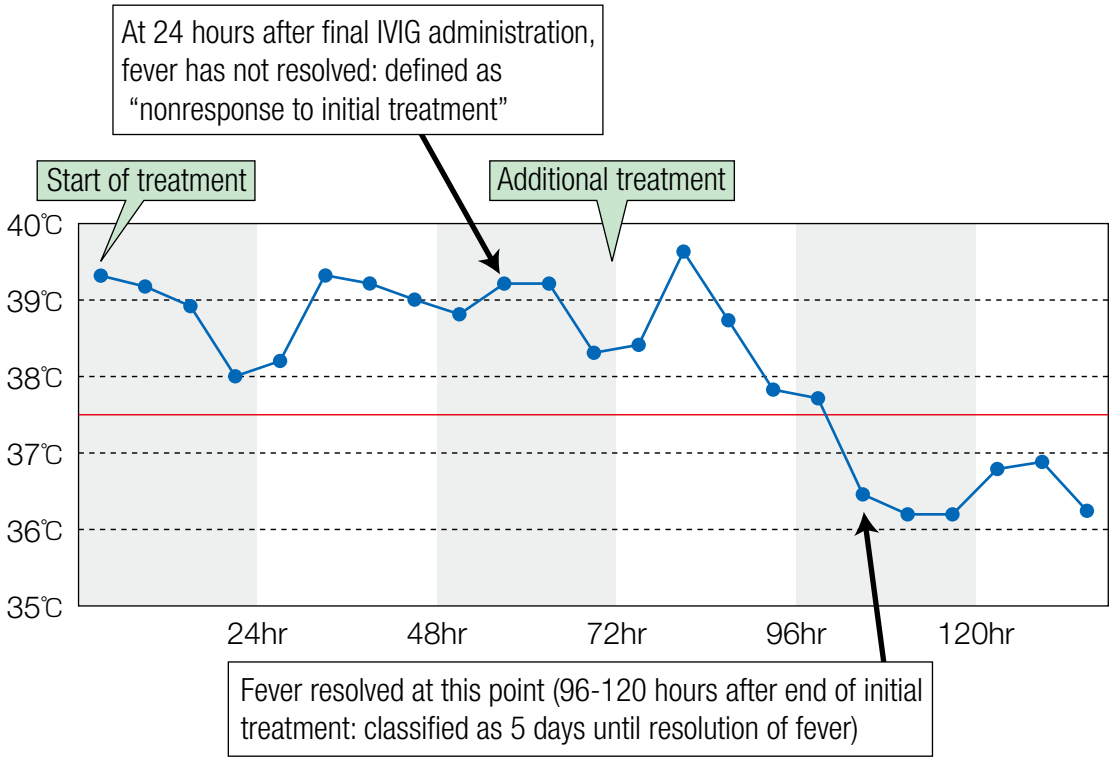




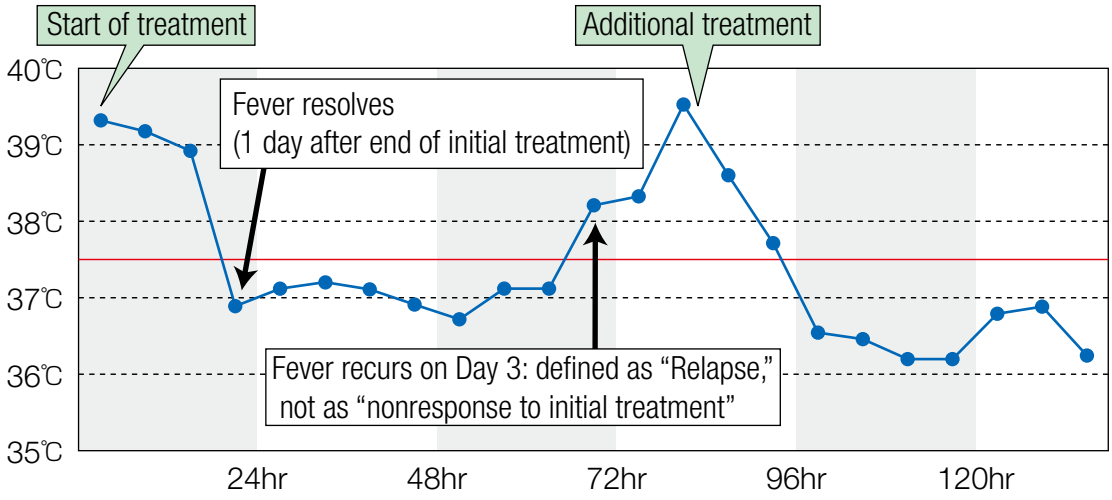
3.4. Definition of treatment nonresponse

Treatment nonresponse is defined as no response to initial treatment, or a relapse.

1. Nonresponse to initial treatment: fever does not resolve within 24 hours after completion of initial IVIG administration.



2. Relapse: fever initially resolves, but then returns, and is accompanied by other symptoms of KD, in the absence of other causes of fever (eg, bacterial or viral infections)



3.5. Definition of coronary artery abnormalities

The coronary artery will be assessed using 2-dimensional echocardiography obtained at baseline, week 1 (6-8 days after enrollment), week 2 (12-16 days after enrollment), and week 4 (24-32 days after enrollment). The coronary artery must be measured at segments 1, 5, and 6. Segments 2, 3, 7, and 11 will also be measured, if possible. Cardiac function and presence of cardiac effusion (more than 1 mm: posterior wall of left ventricle during systole) should also be assessed. All echocardiographic examinations will be recorded from start to finish using a digital video recorder provided by the RAISE Study Office. All examinations will be recorded on DVD and sent to the RAISE Study Data Coordination Center. Using video of digitally recorded 2-dimensional echocardiograms at facilities, all echocardiograms will be interpreted at a core laboratory by 2 pediatric cardiologists blinded to patient identity and illness day. If these cardiologists disagree, a third pediatric cardiologist will make the final decision regarding the presence of abnormalities.

A coronary artery will be defined as abnormal when the luminal diameter is ≥3.0 or ≥4.0 mm in a child aged <5 or ≥5 years, respectively, when the internal diameter of a segment is ≥1.5 times that of an adjacent segment, or when the luminal contour is clearly irregular.[25)]

4. PATIENT SELECTION CRITERIA AND TREATMENT ASSIGNMENT

Eligible patients must fulfill the following inclusion criteria.

4.1. Inclusion criteria

1. Severe KD with a risk score of 5 points or higher
2. Receipt of written informed consent from parents or legal guardians, as per the guidelines of the local institutional review boards that approved the study protocol.
3. Exclusion of other conditions that mimic KD, eg, scarlet fever, Epstein-Barr infection, adenovirus infection, Yersinia infection, measles, and Stevens-Johnson syndrome.

4.2. Exclusion criteria

The following patients will be excluded.

1. Patients who do not provide informed consent for study enrollment
2. Patients with a previous history of KD
3. Patients who present 9 days or later after disease onset (onset defined as first day of fever)
4. Patients with CAA before study enrollment
5. Patients with fever resolution before study enrollment
6. Patients who received corticosteroid in the previous 28 days, either orally, intravenously,

or by intramuscular or subcutaneous injection

7. Patients who received IVIG in the previous 180 days
8. Patients with any of the following severe diseases: immunodeficiency, chromosomal anomalies, congenital heart diseases, metabolic diseases, nephritis, collagen diseases.
9. Patients with suspected infectious disease, including sepsis, septic meningitis, peritonitis, bacterial pneumonia, varicella, influenza, and others.

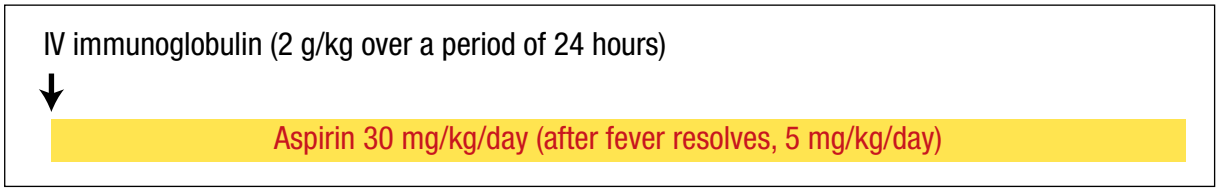
5. TREATMENT PLAN

5.1. Treatment protocol

5.1.1. Initial treatment

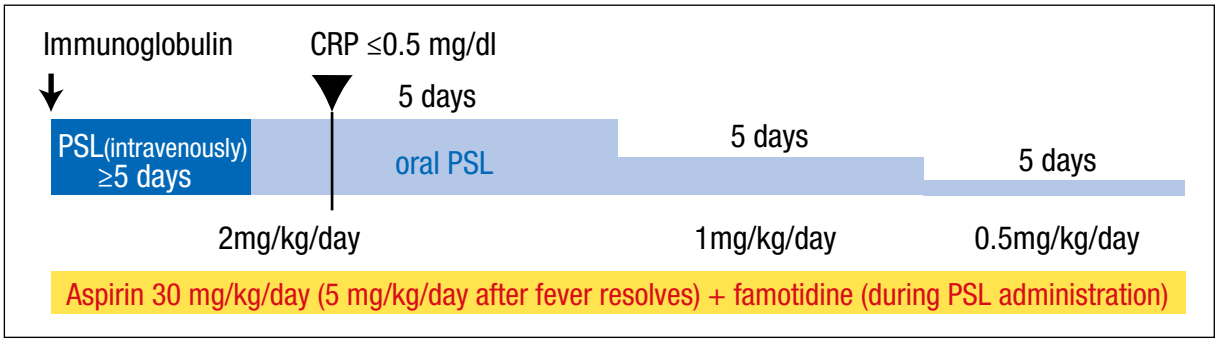
(IVIG Group: treated with IVIG)

Patients will be treated with intravenous immunoglobulin 2 g/kg given over 24 hours. Aspirin will also be given at a dose of 30 mg/kg/day until the patient is afebrile, followed by aspirin 3–5 mg/kg/day until 28 days after enrollment. Aspirin should be continued until 2 months after enrollment



(IVIG+PSL Group: treated with IVIG plus PSL)

Patients in the IVIG+PSL group will also receive the same IVIG with aspirin regimen plus prednisolone sodium succinate (2 mg/kg/day, in 3 divided doses) given by intravenous injection for 5 days. After fever resolves, PSL will be given orally. When CRP level normalizes (≤0.5 mg/dL), the PSL dose will be tapered over 15 days in 5-day steps from 2 to 1 to 0.5 mg/kg/day. Famotidine will be administered with PSL. The maximum dose of PSL is 60 mg/day; thus, patients weighing more than 30 kg will be tapered from PSL 60 to 30 to 15 mg/day.



5.1.2. Prohibited medications

Use of nonsteroidal anti-inflammatory drugs (NSAIDs; e.g. acetaminophen, mefenamic acid) except aspirin and flurbiprofen is not allowed, because a secondary endpoint of the study is days of fever after enrollment, and the use of NSAIDs could influence the results.

5.2. Concomitant therapy

Attending doctors should provide additional rescue therapy for nonresponders, using the recommendations of the "*Guidelines for Acute Phase Therapy for Kawasaki Disease*", promulgated by the Japanese Society of Pediatric Cardiology and Cardiac Surgery in 2003.[26] The following is a general outline of these supplementary treatment modalities.

5.2.1. Treatment options for treatment nonresponse

Although additional rescue therapy for IVIG nonresponders has been examined, the evidence is insufficient due to the lack of a controlled study. In Japan, retreatment with IVIG is the most common rescue therapy. The RAISE Study group allows additional rescue therapy and leaves the choice of such therapy to the attending doctor.

(1)Retreatment with IVIG 2 g/kg or 1 g/kg.

At present, the most common treatment option for nonresponders is retreatment with IVIG. Clinical experience suggests that this is the safest supplementary treatment. The American Heart Association Guidelines recommend a single dose of 2 g/kg IVIG, but no controlled trials have confirmed the efficacy of retreatment with IVIG (Evidence level C).[6]

(2)Corticosteroid (pulsed methylprednisolone and/or PSL)

Corticosteroids are widely used for various forms of vasculitis. However, the use of corticosteroids for KD patients has been limited because of an early report showing a high incidence of CAA in a group that received a prolonged course of oral PSL alone.[11] However, recent reports indicate that treatment with oral or intravenous PSL, or pulsed methylprednisolone, might indeed be effective ether as an initial treatment for all patients or in patients who fail to respond to initial IVIG.[12),13] Some studies have reported that corticosteroid treatment might lead to quicker suppression of serum inflammatory cytokines.[27),28]

(3)Ulinastatin

In Japan, several centers have reported the efficacy of ulinastatin. However, this is an off-label use for the drug, and optimal doses and administration durations are not established. In addition, adverse effects such as rashes and neutropenia have been reported. Ulinastatin should not be simultaneously administered with IVIG via the same route.

(4)Increased dose of aspirin

(5)Nonsteroidal immunosuppressants (eg, cyclosporin A, methotrexate)

Patients unresponsive to IVIG and standard supplementary therapies have been treated

with a variety of immunosuppressants, and occasional case reports have reported successful outcomes.[29),30)]

(6)Anti-TNF α antibodies (e.g. infliximab)

Anti-TNF-α antibodies suppress production of various inflammatory cytokines by specifically blocking TNF α activity. Recently, this treatment was reported to be effective for severe KD patients.[31)-33)] Studies have investigated the use of anti-TNF α antibodies in adults with worsening infectious diseases, such as progressive cardiac insufficiency or recurrent tuberculosis, as well as in infusion events and for treatment of malignant tumors.[34)]

(7)Plasma exchange

Successful use of plasma exchange has been reported in severe KD patients who do not respond to other treatments.[35)]

Treatment	Drug name	Schedule	Adverse effects and other considerations
Corticosteroids	Prednisolone	Start at 2 mg/kg/day, then tapered (as in present study)	Fever might return when dosage is reduced, infection, hypertension, thrombosis, electrolyte imbalance
	Methylprednisolone	10-30 mg/kg/day in 1-3 doses, IV	
Neutrophil elastase inhibitors	Ulinastatin	5000 units /kg; 3-6 times/day, several days IV	Leukopenia, rash
Nonsteroidal immunosuppressants	Cyclosporin A	1-4 mg/kg/day in 2-3 divided doses	Infection, cyclosporin encephalopathy, abnormal liver function, mucous membrane disorders
	Methotrexate	10 mg/body surface area	
Anti-TNFα antibodies	Infliximab	5 mg/kg/day x 1 day, 2-hour IV drip	Shock, worsened cardiac insufficiency, tuberculosis
Plasma exchange (5% albumin solution)		Amount equivalent to circulating blood volume, 1-3 days	Shock, vascular injury

5.3. Withdrawal criteria

1. If a patient is identified as ineligible after enrollment, due to misdiagnosis, misclassification of severity, etc.
2. If the RAISE study office determines that the patient should be excluded due to an unacceptable violation.
3. If the patient or their guarantor requests termination of the protocol treatment.
4. If the patient' s attending physician determines that treatment should be terminated.
5. If a patient dies during the protocol treatment.
6. If the Data and Safety Monitoring Board decides to be terminate the study because of adverse events.
7. If patient information is no longer obtainable due to the patient having changed hospitals, etc.

6. RANDOMIZATION AND ASSIGNMENT ADJUSTMENT

6.1. Case registration

Randomization and allocation of participants is performed via a web-based central allocation system at the University hospital Medical Information Network (UMIN). Among patients that fulfill the inclusion criteria, the attending doctor will explain the study plan to the patients and/or their parents. If informed consent is obtained, the attending physician will enroll the patient after entering the required items (initials of participant, sex, age in months, days of illness at diagnosis, % neutrophils, platelet count, AST, sodium, CRP, and inclusion and exclusion criteria) via the web-based allocation system on the homepage of the RAISE Study. All case registration and group assignment will be done by accessing the Internet home page for RAISE Study researchers: registration and group assignment will not be done by phone or email, except in emergencies. Patient registration and group assignment will be kept on file on the Internet Medical Research Data Coordinating Center (INDICE) server, and online access to this information is possible only through the RAISE Study researcher home page (for security reasons). To access the RAISE Study researchers' site, a UMIN ID and general password are required. To proceed further, to the patient registration page, a UMIN ID and UMIN INDICE password are required.

6.2. Random assignment and assignment adjustment factors

Dynamic random assignment of patients to their respective groups will be done using the minimization method at a 1:1 ratio. The adjustment factors include sex, age, and institution, classified by method of additional rescue therapy (Group A; IVIG retreatment only, Group B; IVIG retreatment and/or conventional dose of PSL, Group C; IVIG retreatment and/or pulsed dose methylprednisolone with or without subsequent PSL, Group D; IVIG retreatment and/or conventional dose of PSL and/or pulsed dose methylprednisolone with or without subsequent PSL and/or infliximab).

7. POSSIBLE ADVERSE EFFECTS AND CLASSIFICATION OF SEVERITY

① Infection

	Minor Adverse Effects	Severe Adverse Effects
Infection	Viral infections without severe symptoms Bacterial infections treatable with oral antibiotics	Viral infections with severe symptoms Bacterial infections curable with intravenous antibacterial administrations

② Allergy/immunity (allergic effects/hypersensitivity)

	Minor Adverse Effects	Severe Adverse Effects
Skin symptoms	Localized urticaria Pruritus	Widespread rash Oculomucocutaneous syndrome Toxic epidermal necrosis Stevens-Johnson syndrome
Systemic symptoms	Angioedema (except pharyngeal edema)	Hypersensitivity syndrome Anaphylaxis Pharyngeal edema

③ Cardiovascular system

	Minor Adverse Effects	Severe Adverse Effects
Hypotension	Asymptomatic hypotension	Symptomatic hypotension
Hypertension	Asymptomatic hypertension	Symptomatic hypertension
Arrhythmia	Supraventricular extrasystole Ventricular extrasystole (single) First-degree atrioventricular block	Supraventricular tachycardia Ventricular extrasystole (couplet or more) Ventricular tachycardia Second- or third-degree atrioventricular block Ventricular fibrillation Torsades de pointes, Cardiac arrest
Impairment of cardiac function	Ejection fraction of left ventricle (on echocardiogram) ≤60%	Ejection fraction of left ventricle (on echocardiogram) ≤40%
Thromboembolism		Deep vein thrombosis, Arterial thrombosis

④ Blood

	Minor Adverse Effects	Severe Adverse Effects
Anemia	20-25% hematocrit	<20% hematocrit
White blood cell count	3000-4000/mm^3	<3000/mm^3
Neutrophil count	1000-2000/mm^3	<1000/mm^3
Platelet count	50,000-100,000/mm^3	<50,000/mm^3
Bleeding	Subcutaneous hemorrhage	Mucosal hemorrhage,Intraorgan hemorrhage

⑤ Skin

	Minor Adverse Effects	Severe Adverse Effects
Ecchymosis	Localized	Generalized
Rash	Limited erythema or papules with no related symptoms	Generalized erythroderma Erythema or papules with itching or other symptoms

⑥ Digestive organs

	Minor Adverse Effects	Severe Adverse Effects
Ulceration	Erosion	Gastric ulcer Duodenal ulcer Hemorrhagic ulcer Perforation of digestive tract
Pancreatitis	Asymptomatic increase in pancreatic enzyme levels	Increase in pancreatic enzyme levels with related symptoms Pancreatic necrosis Hemorrhagic pancreatitis
Enteritis	Frequent bowel movements, Sometimes bloodstained with occasional rectal discomfort	Diarrhea requiring major transfusions Hemorrhagic enteritis
Melena	Positive fecal occult blood testing	Melena accompanied by shock or drop in hemoglobin requiring blood transfusions
Hematemesis	Transfusion not required	Transfusion required
Vomiting	Additional 2 to 5 times as compared with pretreatment average (per 24 hours)	Additional 6 or more times as compared with pretreatment average (per 24 hours)

⑦ Liver

	Minor Adverse Effects	Severe Adverse Effects
Total bilirubin	3.0-9.9 mg/dl	≥10.0 mg/dl
AST, ALT (because these values rise in response to Kawasaki vasculitis, patients should be carefully monitored for increases)	100-499 IU/l	≥500 IU/l
Clinical symptoms, etc.		Jaundice Hepatomegaly Hepatic failure accompanied by bleeding tendency or mental confusion

⑧ Endocrine system/metabolism

	Minor Adverse Effects	Severe Adverse Effects
Hyperglycemia	Asymptomatic hyperglycemia	Symptomatic hyperglycemia
Hypoglycemia	Asymptomatic hypoglycemia	Symptomatic hypoglycemia
Hypercholesteremia	Total cholesterol 220- 399 mg/dl	Total cholesterol ≥400mg/dl

⑨ Bleeding

	Minor Adverse Effects	Severe Adverse Effects
Nasal hemorrhage	Blood transfusion not required	Blood transfusion required
Subcutaneous hemorrhage	Scattered petechiae	Petechiae all over body
Intracranial hemorrhage		Hemorrhage visible on CT or MRI. Intracranial hemorrhage with symptoms

⑩ Musculoskeletal system

	Minor Adverse Effects	Severe Adverse Effects
Arthritis	Mild discomfort accompanying joint Inflammation or swelling with no impairment in normal functioning	Pain (moderate to severe) accompanying joint Inflammation or swelling with normal functioning impaired
Muscular weakness	Asymptomatic Discovered only by medical examination	Related symptoms impair normal functioning
Osteonecrosis	Asymptomatic Visible only on imaging	Related symptoms impair normal functioning

⑪ Neurological disorders

	Minor Adverse Effects	Severe Adverse Effects
Aseptic meningitis	Accompanied only by mild headache and/or vomiting	Cerebrospinal fluid testing reveals increased cerebrospinal fluid cell count, Accompanied by severe clinical symptoms

⑫ Eyes and vision

	Minor Adverse Effects	Severe Adverse Effects
Glaucoma	Increased ocular pressure without visual impairment	Increased ocular pressure accompanied by retinal changes Vision impaired
Cataracts	No clinical symptoms	Clinical symptoms such as visual impairment
Visual disorders	Minor, with no functional impairment	Impairs normal functioning

⑬ Pain

	Minor Adverse Effects	Severe Adverse Effects
Abdominal or joint pain, head or muscle aches	Mild discomfort with no functional impairment	Analgesics required Normal functioning impaired

⑭ Respiratory disorders

	Minor Adverse Effects	Severe Adverse Effects
Cough	General (non-narcotic) antitussive relieves cough	Narcotic antitussive required to relieve cough
Apnea	Oxygenation required	Mechanical ventilation required
Dyspnea, Hypoxemia	Oxygenation required	Dyspnea on exertion and at rest Mechanical ventilation required
Pneumonia	Resolves with standard treatment	Mechanical ventilation required

⑮ Renal and urinary disorders

	Minor Adverse Effects	Severe Adverse Effects
Hematuria	Microscopic hematuria only	Gross hematuria Blood transfusion required
Albuminuria	2+ or lower (qualitative analysis)	3+ or higher (qualitative analysis)
Micturition pain	Mild symptoms, no intervention required	Prominent symptoms requiring treatment
Renal failure	—	Dialysis required

⑯ Others

	Minor Adverse Effects	Severe Adverse Effects
Low body temperature	34.0-35.0°C (axillar)	<34.0°C (axillar)

8. CATEGORIES EVALUATED AND THE SCHEDULE FOR CLINICAL TESTING AND EVALUATION

8.1. Categories evaluated before patient registration

1)Patient background

Age in months, sex, height, weight, date at enrollment, past history of KD

2)Blood testing

Blood count: white blood cell count, % neutrophils, hematocrit, platelet count

Biochemical tests: total bilirubin, AST, ALT, LDH, sodium, potassium chloride, BUN, Cr, total protein, albumin, blood glucose, total cholesterol, HDL cholesterol

Immune serum: CRP, IgG, BNP

3)Urine testing (may be ignored if not collected)

Urine characteristics (sugar, albumin, occult blood), urine sediment

4)Echocardiography

Diameter of coronary artery, left ventricular ejection fraction, presence or absence of valvular disease, presence or absence of pericardial effusion

8.2. Testing and evaluation during study period

1) Laboratory testing: the recommended schedule for laboratory testing is as follows.

- 2 days after enrollment (1 to 3 days after enrollment is allowed)
- 1 week after enrollment (6 to 9 days after enrollment is allowed)
- 2 weeks after enrolment (12 to 16 days after enrollment is allowed)
- 4 weeks after enrollment (24 to 32 days after enrollment is allowed)

Laboratory testing should be performed 2 to 3 times per week until serum CRP level decreases to ≦0.5 mg/dl.

2) Urine testing: as decided by attending physician

3) Echocardiography: the recommended schedule for echocardiography (all echocardiography exams must be digitally recorded)

- 1 week after enrollment (6 to 9 days after enrollment is allowed)
- 2 weeks after enrolment (12 to 16 days after enrollment is allowed)
- 4 weeks after enrollment (24 to 32 days after enrollment is allowed)

4) Adverse events: Daily during the study period.

9. ETHICAL CONSIDERATIONS

9.1. Patient protection

All researchers involved in the present study shall carefully abide by the Helsinki Declaration while conducting this research.

9.2. Informed consent

9.2.1. Explanation given to patients and their families

Before patients are registered, the attending physician will give a copy of an explanatory document (approved by the facility' s IRB) to the patient and/or their family member(s) and verbally explain the details of the procedures to them.

9.2.2. Consent

After the above explanation is given and the patient and/or their family member(s) confirm that they clearly understand the procedures involved, they will be asked if they wish to participate in the study. If the patient or their family member(s) consent to participate in the study, the physician who explained the procedures, together with the patient and/or their family member(s) who consented to participate in the study, will write their names, the patient' s name, and the date consent is given on the attached consent form (or other official consent form approved by the facility). Then, both the physician and patient and/or their family member(s) will sign the form.

9.3. Approval from the facility's ethics review committee (institutional review board)

For participation in the study to be confirmed, the document describing the study procedures, as well as the explanation given to the patient and/or their family member(s), must both be confirmed by the facility' s ethics review committee or IRB

10. DATA COLLECTION

The following documents are to be submitted by fax to the Data Coordinating Center (+81-27-220-8741). They may also be sent by post, in which case the facilities are to retain the original documents and send copies to the Data Coordinating Center. When submitting documents, all names that might permit identification of the patient concerned should be changed to initials. The registration number should be clearly indicated on the form. DVDs or videotapes containing the echocardiographic data should be sent by post to the Data Coordinating Center. If the echocardiographic data contain information permitting identification of the patient (patient name or ID), this information will be masked by the Data

Coordinating Center and rerecorded so as not to permit patient identification, after which the original data will be destroyed.

RAISE Study Data Coordinating Center
Department of Clinical Investigation and Research Unit, Gunma University Hospital
3-39-15 Showa-machi, Maebashi, Gunma, Japan 371-8511
Tel: (+81)-(0)27-220-8740 Fax: (+81)-(0)27-220-8741

10.1. Documents for patient registration, etc.

1) Form for facilities to request permission to participate in the study
2) Form to request patient assignment by fax (if online assignment is impossible)
3) Data sheet
4) Express form for preliminary reports of adverse events
5) Form for full report of adverse events
6) DVD or videotape for recording and submitting patient echocardiogram findings

10.2. Data Cleaning

The Data Coordinating Center will check the registration information and submitted documents. If there are any questions regarding this information, the Data Coordinating Center staff will contact the attending physician by email, fax, or telephone to request necessary clarifications. As for the treatment protocol, any cases in which the treatment or laboratory or echocardiographic examinations may have diverged from the pre-planned acceptable ranges will be reported to the RAISE Study Office for evaluation and judgment. Obvious violations from the protocol will immediately be reported to the RAISE Study Group Principal Investigator (Tsutomu Saji), who will quickly deal with such cases.

11. REPORTING ADVERSE EVENTS

Adverse events should be reported by fax to the Data Coordinating Center.

11.1. Adverse events that must be reported

11.1.1. Adverse events that must be reported immediately

All patient deaths that occur during the protocol treatment or during the 30-day period immediately after the last day of treatment (regardless of whether this was a result of adhering to the treatment protocol)

11.1.2. Adverse events that must be reported at earliest convenience

1) Cases of shock that appear to be related to the administration of the study medication
2) Cases in which the patient contracted a severe infectious disease
3) Hyperglycemia or hypertension accompanied by clear symptoms
4) A body temperature ‹35.0˚C
5) The appearance of eye disorders such as cataracts or glaucoma
6) Thromboembolism
7) Severe hemorrhage
8) Other important clinical phenomena not in the above list but judged to be potentially important should be shared with the RAISE Study Group Principal Investigator, the RAISE Study Office, and other participating facilities

11.2. The duties and procedures of reporting to facility chief investigators participating in this study

There are 2 methods of reporting adverse events: express and standard reporting, which are explained below.

11.2.1. Express report

When an adverse event occurs that requires express reporting, the attending physician should report it to the facility chief investigator as quickly as possible. If it is not possible to contact the chief investigator, the attending physician must report the adverse event. The adverse event shall be reported to the RAISE Study Group Principal Investigator in the following manner.

Initial report :

Within 72 hours of the occurrence of an adverse event, the facility chief investigator will fill in the necessary information in the Adverse Event Preliminary Express-Report Form. After contacting the RAISE Study Office, the facility chief investigator will fax this form directly to the Data Coordinating Center. Because this report should be submitted as quickly as possible, any information requested on the form that is not available at the time it is completed should be left blank. After receiving this preliminary report from the facility, the Data Coordinating Center will then inform both the RAISE Study Office and the RAISE Study Principal Investigator of the details they have received concerning the adverse event.

Secondary report :

The facility chief investigator will then complete the Adverse Event Report Form (Second Express Report), with the more detailed information requested on the form, and fax it to the Data Coordinating Center within 15 days after the appearance of the event. After receiving it, the Data Coordinating Center will then inform the RAISE Study Office and the RAISE Study Principal Investigator of this additional information as quickly as possible. The RAISE Study

Principal Investigator will then quickly inform the Efficacy and Safety Review Board of the event. They will discuss its significance with regard to the progress of the research and future of the RAISE study.

11.2.2. Standard report

Within 15 days of the appearance of the adverse event, the facility chief investigator will complete the Adverse Event Report Form (Final Report) with the required information and fax it to the Data Coordinating Center. After receiving it, the Data Coordinating Center will then inform the RAISE Study Office and the RAISE Study Principal Investigator of any further relevant information as quickly as possible.

11.3. Responsibilities of the RAISE Study Principal Investigator and RAISE Study Office

11.3.1. Judgment of suspension and emergency information to the facilities

When the RAISE Study Principal Investigator receives information from an express report regarding adverse events from facility chief investigators, he will determine the urgency and importance of this information, evaluate its effect on the future of the study, and consider approaches and remedies for it. If immediate action is required, he may contact the Data Coordinating Center and/or facility concerned by telephone; however, this will be followed, as quickly as possible, with a written communication (fax, mail, or e-mail)

11.3.2. Reporting to the Efficacy and Safety Review Board

Once the RAISE Study Principal Investigator has received either the express or final report from a facility about an adverse event, he will determine, based on the list in section 11.1. above ("Adverse events that must be reported"), whether the reported adverse event is indeed one that requires reporting. If it is, after consulting with the RAISE Study Office, he will prepare a written report for the Efficacy and Safety Review Board regarding the event, within 15 days of having been informed of it, inform them of his opinions with regard to the event, and ask the Board to decide whether the clinical response to the event was suitable. This should include the results of his analysis of the adverse event report received from the medical facility, together with how he plans to deal with this information (including whether the study should be continued or terminated).

11.3.3. Analysis of adverse events based on regular monitoring

When regular monitoring is carried out, the RAISE Study Principal Investigator and RAISE Study Office will carefully review reports produced by the Data Coordinating Center regarding adverse events that have been reported, to ensure that no important information has been omitted and is thus still required from the medical facility concerned.

11.3.4. Analysis of the Efficacy and Safety Review Board

The Efficacy and Safety Review Board will inspect and analyze the content of all reports and state in writing its decisions on responses to adverse event to the RAISE Study Principal Investigator, including whether the patient(s) concerned should be removed from the study and whether the treatment protocol should be modified or not.

12. STATISTICS

12.1. Principal analyses and criterion

The main goal of the present study is to determine whether, as compared with standard IVIG treatment, treatment with IVIG plus PSL results in a significant reduction in the primary endpoint, i.e. the incidence of CAA during the study period. To test the null hypothesis (namely, that the incidence of such complications will be the same in both groups), Fisher' s exact test will be used to compare all applicable cases in the 2 groups. Because it is possible that the trial treatment could result in worse outcomes than standard treatment, all testing will be 2-sided. The significance level for all tests will be 5% (2-sided).

If statistical analysis reveals that the incidence of CAA during the study period is significantly lower in the trial treatment group than in the standard treatment group, the conclusion will be that the trial treatment with IVIG plus PSL is the more effective treatment. If no such significant decrease is found, the conclusion will be that treatment with IVIG remains the standard treatment for KD.

12.2. Target number of subjects/ registration period/ follow-up periods

As mentioned in the background of the study (section 2.3.3., "Clinical hypotheses and reason for number of registrants"), the rate of CAA in the IVIG group is expected to be the same as in previous studies of this treatment, ie, approximately 18%. The study design has been established to determine whether the trial treatment (IVIG plus PSL) can achieve at least an additional 10% absolute reduction in the incidence of CAA during the study period, i.e. reduce the incidence rate to 8% or less. If the study requires a 3-year registration period and a 1-month follow-up period, and α is equal to 5% (2-sided) with a statistical power of 80%, the number of cases required for each group will be 176, for a total of 352 in the 2 groups. If a 10% drop-out rate is assumed, the final enrollment numbers are as follows.

Target number of subjects: 196 per group, for a total of 392 patients.

Registration period: 3 years. Follow-up period: 1 month after enrollment.

12.3. Interim analysis and early termination of study

12.3.1. Purpose and timing of the interim analysis

One interim analysis is planned to evaluate whether the study is achieving its principal objectives. The purpose of this interim analysis will be to decide on the suitability of continuing to enroll patients in the study. If it is determined that the principal objectives of the study have been achieved, then the study will be terminated and its results reported at conferences and published in relevant journals as quickly as possible.

The interim analysis will be started after the first year of the study has been completed, using the initial monitoring data accumulated since the start of the study. In the event that 200 patients have not yet been enrolled in the study at 1 year after initiation of the study, the interim analysis will be done when data for 200 patients become available. Finally, as a rule, patient enrollment will continue while the interim analysis is being conducted.

12.3.2. Method of interim analysis

The interim analysis will be carried out by the staff of the RAISE Study Statistical Center. To keep overall α error of the RAISE study below 5%, the Lan-DeMets α-spending function[36] with the O' Brien-Fleming monitoring boundaries was used to adjust for multiple comparisons. Differences in values between the 2 study groups will be analyzed to determine if they are statistically significant or not. If the interim analysis reveals a lower rate of CAA during study period in the group receiving IVIG plus PSL as compared with the group receiving standard IVIG and Fisher' s exact test yields a p value <0.0034, this will be considered sufficient statistical evidence to accept the study' s main hypothesis and, barring other important considerations, the study will, in principle, be terminated.

12.3.3. Reporting and evaluating the interim analysis results

The report of the interim analysis will be submitted to the Efficacy and Safety Review Board, which will decide whether the study should be terminated or not. Based on the results of the interim analysis, the Efficacy and Safety Review Board will discuss the continuation of the study at the Steering Committee and inform the RAISE Study Principal Investigator of the decisions they have reached with respect to continuation of the study and publication of its results. If, based on careful review of the interim-analysis report, the Efficacy and Safety Review Board decides that all or part of the study should be terminated or its protocol changed, the RAISE Study Principal Investigator will carefully consider this recommendation and issue a final decision as to whether to terminate the study or change part of its protocol. If the study is to be terminated or continued with an amended protocol, the RAISE Study Principal Investigator will submit the corresponding documents to the Efficacy and Safety Review Board: either the Request for Permission to Terminate the Study or Request for

Protocol Amendment, respectively. Once permission is granted by the Efficacy and Safety Review Board, the study may be terminated or its protocol amended.

12.4. Analysis of secondary endpoints

Analysis of the secondary endpoints will also be carried out to provide additional data for consideration of the results of the principal analysis of the study. Correction for the multiplicity of tests will not be performed because of the exploratory nature of the secondary endpoints. Comparisons between groups will be performed as necessary, but it is important to note that, although no statistically significant differences can be reported, this should not be interpreted to mean that there are no real differences between the treatment groups.

12.4.1. Analysis of the secondary endpoint related to safety

Of the several secondary endpoints studied, the endpoint related to safety is based on the incidence of adverse events, and this endpoint will therefore require regular monitoring.

12.4.2. Analysis of secondary endpoints related to efficacy

The secondary endpoints related to treatment efficacy include incidence of CAA at week 4 after enrollment, Z scores for the right coronary artery and left main coronary trunk and anterior descending artery, days of fever after enrollment, incidence of need for additional rescue therapy, and serum levels of CRP at Weeks 1 and 2 after enrollment. These secondary endpoints will only be analyzed during the interim analysis and at the end of the study, and only as secondary endpoints; there will be no correction for the multiplicity of tests when these endpoints are analyzed.

It is expected that the incidence of CAA at week 4 after enrollment will be lower in the IVIG plus PSL group than in the IVIG group, as this result is expected to be correlated with the largest diameter attained during the enlargement of the coronary artery, while these treatments are being administered.

As for incidence of need for additional rescue therapy, this can be considered to reflect the effectiveness of the treatments. It is therefore expected that this incidence will be lower in the IVIG plus PSL group than in the IVIG group.

As for days of fever after enrollment and serum levels of CRP at Weeks 1 and 2 after enrollment, these can be considered endpoints that depend on the suppression of KD vasculitis achieved by the treatments. It is therefore expected that, as compared with standard IVIG treatment, the period required for days of fever after enrollment will be shorter, and that serum levels of CRP at Weeks 1 and 2 after enrollment will be lower, in the IVIG plus PSL group.

Fisher' s exact test will be used to evaluate the incidence of CAA at Week 4 after enrollment

and the incidence of need for additional rescue therapy; the interval estimation will be done with exact confidence intervals based on the binomial distribution.

Z scores for the right coronary artery and left main coronary trunk and anterior descending artery, days of fever after enrollment, and serum levels of CRP at Weeks 1 and 2 after enrollment will first be tested for normality with the Kolmogorov-Smirnov test. Variables that are found to have a normal distribution will be compared using the unpaired t-test; those with a non-normal distribution will be compared using the Mann-Whitney U-test.

12.5. Termination of the study if the incidence of giant coronary aneurisms in the trial treatment group is high

In general, the most important goal in treating KD patients is to prevent giant coronary aneurysms, which require lasting medical treatment. Thus, if the incidence of giant coronary aneurysms is higher for patients receiving the trial treatment than for those receiving the standard treatment, the trial treatment will be considered ineffective in reducing the incidence of such aneurysms and the study will be promptly terminated.

In the most recent national survey in Japan, the incidence of giant coronary aneurysms was 0.35%.[7] If we assume that these patients would be stratified as high-risk patients, the incidence of giant coronary aneurysm among patients in this study could ultimately be as high as 1.1%. Therefore, if 4 patients in the trial treatment group develop giant coronary aneurysms, the Data Coordinating Center will immediately report this fact to both the RAISE Study Principal Investigator and the Efficacy and Safety Review Board, and the Board will then carefully review the cases and decide whether the study should be terminated.

12.6. Final Decision

When the follow-up period is completed and all the results of the final investigations have been determined, an analysis of all the study endpoints will be conducted. Until then, there will be no comparisons between groups with respect to either the primary endpoint or the secondary endpoints concerned with treatment effectiveness, unless such comparisons are added to the study protocol or special permission is received from the Efficacy and Safety Review Board.

The final results of all analyses will be assembled by the Data Coordinating Center into a Final Analysis Report, which will be submitted to the RAISE Study Office and the RAISE Study Principal Investigator. The RAISE Study Principal Investigator and the RAISE Study Office will then write a Summary Report for the use of clinical practitioners, based on the summarized contents of this Final Analysis Report, after careful consideration of the general conclusions of the study and an analysis and discussion of its problems and results, as well as suggestions for further research in this area. The study will then be considered finished.

13. ETHICAL CONSIDERATIONS

13.1. Patient protection

All researchers involved in the present study will strictly abide by the Helsinki Declaration in carrying out all the procedures of this study.

13.2. Informed consent

13.2.1. Explanation given to patients and their families

Before the patient is enrolled in the study, their attending physician will give the patient and/or the patient's family an explanatory document that has been approved by the IRB of that facility. If the patient is younger than 16 years, this document is to be handed to their guardian, and the following details are to be verbally explained:

1. The diagnosis of KD, its severity, and an explanation regarding its prognosis
2. The fact that they have the option of being enrolled in a clinical trial, with a detailed explanation of the difference between the meanings of "clinical trial" and "clinical practice"
3. The study design and its rationale (including its importance, the number of patients to be enrolled, its necessity, and its goals)
4. The content of the treatment protocol (the names and doses of the drugs to be administered, methods of administration, total duration of treatment and follow-up, and other important details, as requested)
5. The expected effect of the protocol treatment
6. Possible adverse events, complications, and sequelae, and clinical responses to these (known severity and incidence rates of various adverse events, as well as the clinical responses that will be undertaken in the event of their occurrence)
7. Responsibility for treatment costs and compensation (the physician will explain that the costs of the treatment will be covered by insurance, and that if permanent health problems arise from participating in the study, that compensation will be paid, the amount of which shall be equivalent to the compensation given for such events if they had arisen as a result of general medical practice)
8. The expected advantages and possible disadvantages to the patient arising from participation in the study
9. Access to patient medical history (an explanation of the external inspection of patient data, eg, "To ensure quality control, medical personnel from other facilities may receive permission from our hospital president to have direct visual access to patient medical records.")

10. Non-consent and withdrawal of consent (the fact that they are free to decline to participate in the study before the patient is enrolled and that, even after enrollment, they remain free at any time to withdraw from the study, and that such withdrawal will not in any way lessen the quality of care the patient receives)
11. Protection of human rights (the fact that all involved in the study will do their utmost to guarantee the confidentiality of the patient's identity and personal information)
12. The reuse of patient information (the possibility that the patient's data may be reused for scientific research, such as in meta-analyses, etc.), while maintaining patient anonymity
13. The right to ask questions (the patient and/or guardian(s) will be provided with a written document containing contact information for the attending physician, the facility chief investigator, and the RAISE Study Principal Investigator [and/or the RAISE Study Office]. The patient and/or guarantor(s) shall be informed that they are free to contact them and ask them any questions they might have, whether about the study or the treatment protocol).

13.2.2. Consent

After the patient and/or guarantor(s) have received the above explanations and have had a chance to confirm that they have indeed understood the contents of the study, they will be asked to participate in the study. If they consent to do so, the names of the physician who explained the above information and the patient and guarantor who consent to participate in the study will be written on the consent form appended to this protocol (or other suitable consent form as determined by the physician's institution), after which the physician and patient or guarantor will sign the document and add the date consent was given. Two copies will be made of this consent form, with one being given to the patient and/or guarantor(s), and one being retained by the facility coordinator. The original document will be kept in the file with the patient's medical records.

13.3. Protection of privacy and patient identification

The patient's full name will never be communicated to the Data Coordinating Center by the participating facility where s/he is receiving treatment. All references to patient identity will use the case number received at the time of patient registration and the patient's initials. The medical staff at the facility where the patient is being treated will know the patient's name, but there will be no record in the database at the Data Coordinating Center of personal information that could potentially be used by a third party to directly identify the patient.

13.4. Treatment in strict accordance with the study protocol

All investigators participating in the present study will strictly abide by all the rules detailed in this study protocol, except in cases where respecting these rules would require the investigators to endanger the patient or infringe upon the patient' s human rights.

13.5. Approval by the Ethics Committee (Institutional Review Board) of each participating facility

13.5.1 Approval must be received before the facility can participate in the study

In order for a facility to participate in the study, this study protocol, together with the document that explains the treatment procedure to the patient and their family members, must be approved by that facility' s Ethics Committee or Institutional Review Board (IRB). Once approval has been given by the facility' s IRB, the facility coordinator shall fax a copy of the document showing their IRB approval to the Data Coordinating Center and keep the original document on file at their own facility.

14. MONITORING AND AUDITING

14.1. Regular monitoring

Regular monitoring will be carried out twice a year to guarantee the safety of the study subjects by ensuring study protocol adherence with regard to patient treatment and to confirm that all data are being correctly collected.

Central monitoring will be done with the aid of the information entered on the data sheets and collected at the Data Coordinating Center. If the Data Coordinating Center deems it necessary, onsite monitoring may also be done—by visiting respective facilities and comparing the original documents retained at these facilities with information stored in the Data Coordinating Center—together with other monitoring activities as required.

The Data Coordinating Center will produce regular Monitoring Reports and submit these reports to the RAISE Study Office, the RAISE Study Principal Investigator, and the Efficacy and Safety Review Board.

14.1.1. Monitoring items

The following items will be monitored:

1) Whether planned enrollment numbers are being reached: the number of patients enrolling during any given period and the cumulative number of patients enrolled at any given point, for all facilities and at each individual facility
2) Eligibility: the ineligibility and possible ineligibility of certain patients, per group and per facility

3) Differences during and after receiving the protocol treatment, per group and per facility
4) Background factors before enrollment, per group
5) Severe and minor adverse events, per group and per facility
6) Protocol violations, per group and per facility
7) Other points as required, including the general progress of the study and safety concerns

14.1.2. Protocol deviations and violations

If the administration of medication, conduct of clinical tests, evaluation of the toxicity or efficacy of therapy, or the conduct of any other clinical procedure or medical treatment is not faithfully carried out according to the protocol detailed in this document, it shall be deemed a deviation of protocol.

On monitoring, any deviations from the study protocol that exceed what the Data Coordinating Center, together with the RAISE Study Principal Investigator and RAISE Study Office, deem acceptable, on a case-by-case basis, will be included in a list of Cases of Possible Protocol Deviations to be included in the monitoring report. The RAISE Study Office and RAISE Study Group will then carefully analyze these deviations and classify them according to the following classification scheme:

Violations

As a rule, any deviation that satisfies 2 or more of the following conditions will be considered a violation of the study protocol:

1) A deviation that makes evaluation of an endpoint problematic or impossible
2) A deviation caused by the attending physician or the facility concerned
3) A deviation that was intentional or systematic
4) A deviation that was dangerous or differed greatly from the study protocol
5) A deviation that was clinically inappropriate

In general, the specific content of each of these violations will be described in detail in published papers describing the study.

Acceptable deviations

Acceptable deviations are those deviations that remain within the limits of what had been agreed to, on a case-by-case basis, by the Data Coordinating Center in consultation with the RAISE Study Principal Investigator and RAISE Study Office, and shall be regarded as permissible deviations from the standard protocol (either before or after the deviation occurred). Deviations that remain within acceptable limits, agreed to before the deviation occurred, will not be noted in the monitoring report.

Deviations

Deviations will be defined as anomalies when they are not classified as either of the above 2

categories, ie, violations or acceptable deviations. If a particular anomaly occurs often during the study, it will be noted in future articles reporting the findings of the study.

14.2. Onsite inspection of facilities

Facilities participating in the study will be visited and inspected to maintain and improve the study's scientific and ethical conduct. The inspector will visit participating facilities as required, examine that facility's original IRB document approving its participation in the study and the original consent forms signed by the patients, compare the information on each patient's data sheet with their actual medical records kept at the facility, and effect other inspections as deemed necessary. The results of these facility inspections will be reported to the research coordinator of the given facility, and to the Data Coordinating Center, RAISE Study Office, and RAISE Study Principal Investigator. If the details of such inspections are ever made public, the name of the facility in question will not be revealed.

15. REPORTING THE STUDY RESULTS

When reporting the results from the study at conferences and in written publications, all existing policies established by the steering committee relating to such reporting will be respected and adhered to. If no clear policies have been decided upon at the time of reporting, it shall be done in accordance with the following conditions:

All principal reports describing the study will be written only after the final analysis has been done and will be submitted to English-language journals for publication.

Except in the case of written permission given by the Efficacy and Safety Review Board, no findings of this study will be made public until either the final analysis described in the protocol has been completed or an interim analysis has been carried out for the express purpose of reporting its findings, as described in the study protocol. However, the RAISE Study Principal Investigator, or the RAISE Study Office with the permission of the RAISE Study Principal Investigator, may present relevant findings at academic conferences or publish articles for the purpose of introducing the study to a wider audience, without including the actual results of an analysis of the endpoints of the study.

In principle, the main reports describing the results of the study will list the RAISE Study Office as the first author. After that, in order, will be listed the RAISE Study Principal Investigator and the person in charge of the statistical analysis required to report the results. After that, in accordance with the limits placed on the number of authors of written reports, coauthors will include members of the steering committee and the facility chief investigator (or facility coordinators) of the facilities that had the most patients enrolled in the study, listed in

descending order of enrollment.

All coauthors will have an opportunity to review the content of the finished report before it is submitted for publication and only those who agree with it will be listed as coauthors on the final manuscript. If a researcher who was involved in the study disagrees with part of the manuscript, even after discussing their opinion with other authors, the RAISE Study Principal Investigator reserves the right to exclude this researcher as a coauthor in the final version of the manuscript.

Because the study contents might be presented several times at various conferences, the RAISE Study Office, RAISE Study Principal Investigator, and the facility chief Investigator/ facility coordinator at the facilities that had the most patients involved in the study will share the responsibility of making such presentations, and the RAISE Study Principal Investigator will decide who will have the right to publically present the study findings. However, when the study results are presented at academic conferences, the RAISE Study Office will be responsible for preparing the presentation and determining its content and will assemble this information with the assistance of the Data Coordinating Center. Presenters other than those in the RAISE Study Office will not have direct access to the data and analysis results on file at the Data Coordinating Center, except with the written permission of both the RAISE Study Office and the Head of the Data Coordinating Center.

16. RAISE Study Group

16.1. Principal Investigator

Tsutomu Saji

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TEL : +81-3-3762-4151
FAX : +81-3-3298-8217
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16.2. RAISE Study Office

Gunma University Graduate School of Medicine, Department of Pediatrics
Chief: Tohru Kobayashi

3-39-22 Showa-machi, Maebashi, Gunma, 371-8511, Japan
TEL : +81-27-220-8205　Mobile : 090-9101-1996
FAX : +81-27-220-8215
E-mail : raise-discussion@umin.ac.jp

16.3. Data Coordination Center

Gunma University Hospital, Department of Clinical Investigation and Research Unit

3-39-15 Showa-machi, Maebashi, Gunma, 371-8511, Japan
TEL : +81-27-220-8740
FAX : +81-27-220-8741
Chief : Tetsuya Nakamura
Data Managers : Mami Okada, Sayuri Fukushima, Atsushi Matsumoto, Etsuko Saito, Fumie Tokuda

16.4. Data and Safety Monitoring Board

Chief: Takeshi Tomomasa
PAL Children' s Clinic

3303-2, Tsunatori-machi, Isesaki, Gunma, 372-0812, Japan
E-mail : tomomasa@gunma-u.ac.jp

16.5. Steering Committee of RAISE Study

Tsutomu Saji	Toho University Omori Medical Center
Tomoyoshi Sonobe	Japan Red Cross Medical Center
Akihiro Morikawa	Gunma University Graduate School of Medicine
Kenji Hamaoka	Kyoto Prefectural University of Medical Graduate School of Medhical Science
Toshiro Hara	Kyusyu University Graduate School of Medical Sciences
Shunichi Ogawa	Nippon Medical School
Hirokazu Arakawa	Gunma University Graduate School of Medicine
Kazuo Takeuchi	Saitama University
Fukiko Ichida	Toyama University
Jun Abe	Center for Child Health and Development
Tetsuya Nakamura	Gunma University Hospital
Yuichi Nomura	Kagoshima University Graduate School of Medical and Dental Science
Masaru Miura	Tokyo Metropolitan Children's Medical Center
Mamoru Ayusawa	Nihon University
Yoshihiro Onouchi	RIKEN
Yoshinari Inoue	Inoue Children' s Clinic
Taichi Kato	Nagoya University Graduate School of Medicine
Tohru Kobayashi	Gunma University Graduate School of Medicine
Tetsuya Otani	Center for Child Health and Development

17. REFERENCES

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